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(71) Applicant: **JOHNSON & JOHNSON CONSUMER  
COMPANIES, INC.**  
**Skillman, NJ 08558 (US)**

(72) Inventors:

- **Kung, John**  
**Somerset, New Jersey 08873 (US)**
- **Liu, Jue-Chen**  
**Belle Mead, New Jersey 08502 (US)**

(74) Representative: **Fisher, Adrian John**  
**CARPMAELS & RANSFORD**  
**43 Bloomsbury Square**  
**London WC1A 2RA (GB)**

(54) **Compositions for stabilizing oxygen-labile species**

(57) This invention relates to compositions and methods for stabilizing oxygen-labile species. More particularly, it relates to compositions containing one or

more oil- and/or water-soluble oxygen-labile species and one or more stabilizing elements. It also relates to methods of making such compositions and methods of using such compositions.

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**Description**

[0001] Reference to copending patent applications: This patent application is being filed simultaneously with U.S. Patent Application Serial No. \_\_\_\_\_ (Attorney Docket No. NEU-017; inventors Christopher Stahl and Frederick Woodin) and hereby incorporates herein the disclosure of such patent application by reference.

**Field of the Invention**

[0002] This invention relates to compositions and methods for stabilizing oxygen-labile species in compositions. More particularly, it relates to compositions containing one or more oil- and/or water-soluble oxygen-labile species and one or more stabilizing elements. It also relates to methods of making such compositions and methods of using such compositions.

**Background of the Invention**

[0003] For many years, it has proven difficult to make stable compositions containing oxygen-labile species. "Oxygen-labile" species are those that are easily oxidized and readily decompose when exposed to the environment. Such oxygen-labile species are, therefore, very difficult to formulate into compositions in combination with other compounds that may accelerate such decomposition or that may be exposed to the environment over time. In recent years, it has become desirable, for example, to include various vitamin compounds in topical skin care compositions in order to nourish or repair the skin. However, those of ordinary skill in the art have found that these vitamin compounds are quite unstable in topical compounds due to the fact that they are easily oxidized and decompose quickly, resulting in loss of efficacy and discoloration of the composition.

[0004] Thio compounds such as metabisulfite and sulfite compounds have been known as good water-soluble anti-oxidants and have been added to compositions to prevent such oxidation problems. However, these compounds may cause sensitization in certain individuals and are not useful for administration to humans. They also possess noxious odors and are unpleasant to use. Japanese Patent Publication No. 53-7488, for example, suggests that combining ascorbic acid with dl-N-acetyl homocysteine thiolactone or N-acetyl-L-cysteine and sulfite in an aqueous solution of ascorbic acid results in a composition that can be stored stably over a long period.

[0005] EP 0 349 797 B1 mentions the combination of N-acetylcysteine and ascorbic acid or ascorbate as a stabilizer for the N-acetylcysteine. Slovakian publication, Farm. Obzor - LIV - 1985 p. 513 (Pharmacology Review) mentions the combination of N-acetylcysteine and ascorbic acid at a pH of 6.2. Both N-acetylcysteine and ascorbic acid are water-soluble. However, none of these references indicate that N-acetylcysteine would serve to stabilize an oil-soluble oxygen-labile species.

[0006] Thus, it is an object of this invention to provide compositions that contain oxygen-labile species that are stable over long periods of time.

[0007] It is another object of this invention to provide compositions that contain oil-soluble and/or water-soluble oxygen-labile species that are stable over long periods of time.

[0008] Yet another object of this invention is to provide compositions that contain both oil-soluble and water-soluble oxygen-labile species that are stable over long periods of time.

[0009] It is another object of this invention to provide methods of making stable compositions containing oxygen-labile species.

[0010] Another object of this invention is to provide methods of using the stable oxygen-labile species-containing compositions of this invention.

[0011] Yet another object of this invention is to provide skin care compositions that contain oxygen-labile species such as vitamins and their derivatives for topical use on the skin.

**Summary of the Invention**

[0012] We have discovered that certain oil-soluble and/or water-soluble oxygen-labile species may be stabilized in compositions by the addition of one or more stabilizer compounds. Such stabilizer compounds are selected from the following categories:

- a) thio-containing compounds, such as sulfites and cysteine derivatives; and
- b) glycoproteins, such as lactoferrin.

Oil-soluble oxygen-labile species may include vitamin compounds such as retinoids, choleciferol, vitamin K, tocotrienol and tocopherol derivatives, essential fatty acids and the like. Water-soluble oxygen-labile species may include vitamin

compounds such as ascorbic acid and its derivatives, niacin, thiamine, riboflavin, folic acid, pyridoxine, pantothenic acid, niacinamide, lipoic acid, dihydrolipoic acid, essential amino acids and the like. The oil-soluble oxygen-labile species may be present in the compositions of this invention in amounts of from about 0.01 to about 10%. The water-soluble oxygen-labile species may be present in the compositions of this invention in amounts of from about 0.01 to about 20%.

### **Detailed Description of the Preferred Embodiments**

**[0013]** The compositions of this invention contain certain oil-soluble and/or water-soluble oxygen-labile species which are stabilized in compositions by the addition of one or more stabilizer compounds. Such stabilizer compounds are selected from the following categories:

- a) thio-containing compounds, such as sulfites and cysteine derivatives; and
- b) glycoproteins, such as lactoferrin.

The stabilizers which are included in the term "thio-containing compounds" include such compounds as sulfites and metabisulfites, cysteine derivatives and glutathione. More preferably, the thio-containing compounds are cysteine derivatives. Most preferably, the thio-containing compound is N-acetylcysteine. Thio-containing compounds are well-known as stabilizers of water-soluble compounds as they reside in the water phase of compositions. However, they are not known to be capable of stabilizing oil-soluble compounds as they do not reside in the oil phase of compositions. Surprisingly, we have found that compositions containing both water- and oil-soluble oxygen labile species as well as thio-containing compounds are stable over long periods of time. Preferably, the amount of thio-containing compound should range from about 0.001 to about 5% of the weight of the composition. More preferably, there should be from about 0.01 to about 0.5% of the composition by weight.

**[0014]** Furthermore, compositions containing oil-soluble and/or water-soluble oxygen labile species and stabilizer compounds, selected from the group of glycoproteins are surprisingly stable. The glycoproteins that are useful in the compositions of this invention include lactoferrin and the like. Unexpectedly, such glycoproteins, large molecules that reside in the water phase of compositions, and which are known to be biologically active have proven to be viable as stabilizer compounds in the compositions of this invention. Although it is unknown how these proteins serve to stabilize the compositions of this invention, it is theorized that the proteins may reside at the oil/water interface of the compositions of this invention and are therefore active in both phases. Alternatively, the proteins may somehow adsorb or attract the ions that would otherwise cause oxidation of the oxygen-labile species of the compositions of this invention. Preferably, the amount of glycoprotein compound should range from about 0.00001 to about 5% of the weight of the composition. More preferably, there should be from about 0.01 to about 1% of the composition by weight.

**[0015]** Most preferably, the glycoprotein useful in the compositions of this invention is lactoferrin, a milk-derived protein that chelates iron and has a molecular weight of 80,000 daltons. Although lactoferrin is known as an anti-free radical compound in biological systems, it has heretofore been unknown for use in formulations. Whether an antioxidant or chelator which is active in a biological system will be active in a composition is completely unpredictable.

**[0016]** The oxygen-labile species may exist in the compositions of this invention either individually or as a combination. For example, vitamins A, C or E may be present in the compositions of this invention individually, i.e., one of such vitamins in one composition. Alternatively, various combinations of vitamins may be present within an individual composition, for example, vitamin C (ascorbic acid) may be present in a composition with either thio-containing compounds, such as sulfites and cysteine derivatives or a glycoprotein, such as lactoferrin or both. Vitamins A and C may be present within an individual composition with thio-containing compounds, such as sulfites and cysteine derivatives or a glycoprotein, such as lactoferrin or both to achieve a stable formulation. Vitamins C and E may be present within an individual composition with thio-containing compounds, such as sulfites and cysteine derivatives or a glycoprotein, such as lactoferrin or both. Vitamins A, C and E may also be present in an individual composition with thio-containing compounds or a glycoprotein or both. Surprisingly, in each of these compositions, both the water-soluble and oil-soluble oxygen-labile species are stable over a long period of time. One of ordinary skill in the art would expect that vitamins A and C together would not be stable as Vitamin C tends to sacrifice itself to stabilize Vitamin A. Compositions of this invention containing both Vitamins A and E together, we have found, preferably contain at least about 0.0001% of Vitamin C for ensuring stability of all materials.

**[0017]** The compositions of this invention may be utilized in dosage forms suitable for cosmetic or pharmaceutical use. For example, the compositions of this invention may be made in the forms of emulsions, creams, lotions, gels, essences, milks, toners, hydroalcoholic solutions, multivesicular systems, suspensions, patches, masks, sticks, and other dosage forms suitable for therapeutic use, including oral administration forms.

**[0018]** The compositions of this invention may be made using conventional formulation technology. For example, in a standard oil-in-water emulsion, the starting water phase should be purged with either nitrogen or argon to displace

any residual oxygen. Alternatively, the water phase may be heated to 80°C and held at that temperature at least about ten minutes to reduce oxygen solubility. A conventional oil phase should be made and the oil phase poured into the water phase. After phasing, the formulation should be blanketed with an inert gas such as nitrogen or argon and the formulation permitted to cool to room temperature. As the temperature reaches 45° C, the stabilizer compound should be added to the formulation. The stabilizer compound should be mixed into the formulation for about ten minutes, after which the oxygen-labile species may be introduced into the formulation. Neutralization to the appropriate pH may be made prior to or subsequent to the addition of the oxygen-labile species, depending upon the oxygen-labile species utilized. For example, neutralization is preferred subsequent to adding ascorbic acid, but should be accomplished prior to adding retinol. The formulation resulting from this process should be packaged in an oxygen-impermeable package, such as an aluminum tube.

**[0019]** The pH of the formulations of this invention is preferably in a range that is suitable for a particular oxygen-labile species used in the compositions. The pH should reflect as closely as possible the physiological pH of the skin without compromising the chemical stability of the oxygen-labile species. For example, the preferred pH environment for ascorbic acid should about 5.5 and above. The preferred pH for retinol should be about 5.5 and above. Preferably, the pH should be between about 5.5 and about 9. pH greater than about 10 may result in irritation to the skin when applied topically.

**[0020]** During manufacture of the compositions of this invention, oxygen exposure should be minimized as much as possible so as to reduce the possibility of oxidizing the oxygen-labile species and preserve its stability. Therefore, to the extent possible, all oxygen in the manufacturing system should be displaced with nitrogen or argon gas, as set forth, for example, in U.S. Patent No. 5,559,149.

**[0021]** The compositions of this invention may be used in therapeutic situations wherever the oxygen-labile ingredients are therapeutically active. For example, ascorbic acid can be used for collagen synthesis, elastin synthesis or skin depigmentation and other known uses. Tocopherol, for example, may be useful in free radical scavenging internally or topically. The compositions of this invention may be applied topically to the skin on a daily or more or less frequent basis. The compositions of this invention deliver therapeutic quantities of oxygen-labile species to the skin.

**[0022]** Other emollients and surface active agents have been incorporated in the emulsions, including glycerol trioleate, acetylated sucrose distearate, sorbitan trioleate, polyoxyethylene (1) monostearate, glycerol monooleate, sucrose distearate, polyethylene glycol (50) monostearate, octylphenoxypoly (ethyleneoxy) ethanol, decaglycerin penta-isostearate, sorbitan sesquioleate, hydroxylated lanolin, lanolin, triglyceryl diisostearate, polyoxyethylene (2) oleyl ether, calcium stearoyl-2-lactylate, methyl glucoside sesquisteate, sorbitan monopalmitate, methoxy polyethylene glycol-22/dodecyl glycol copolymer (Elfacos E200), polyethylene glycol-45/dodecyl glycol copolymer (Elfacos ST9), polyethylene glycol 400 distearate, and lanolin derived sterol extracts, glycol stearate and glycerol stearate; alcohols, such as cetyl alcohol and lanolin alcohol; myristates, such as isopropyl myristate; cetyl palmitate; cholesterol; stearic acid; propylene glycol; glycerine, sorbitol and the like.

**[0023]** The composition of this invention can contain additives, as required, such as a humectant, an antioxidant, a preservative, a flavor, fragrances, a surface active agent, a binder, and the like, as well as skin protectant agents, therapeutic agents and "cosmeceuticals".

**[0024]** Examples of the preservatives include salicylic acid, chlorhexidine hydrochloride, phenoxyethanol, sodium benzoate, methyl para-hydroxybenzoate, ethyl para-hydroxybenzoate, propyl para-hydroxybenzoate, butyl parahydroxybenzoate and the like.

**[0025]** Examples of the flavor and fragrance include menthol, anethole, carvone, eugenol, limonene, ocimene, n-decylalcohol, citronellol, a-terpineol, methyl salicylate, methyl acetate, citronellyl acetate, cineole, linalool, ethyl linalool, vanillin, thymol, spearmint oil, peppermint oil, lemon oil, orange oil, sage oil, rosemary oil, cinnamon oil, pimento oil, cinnamon leaf oil, perilla oil, wintergreen oil, clove oil, eucalyptus oil and the like.

**[0026]** Examples of surface active agents include sodium alkyl sulfates, e.g., sodium lauryl sulfate and sodium myristyl sulfate, sodium N-acyl sarcosinates, e.g., sodium N-lauroyl sarcosinate and sodium N-myristoyl sarcosinate, sodium dodecylbenzenesulfonate, sodium hydrogenated coconut fatty acid monoglyceride sulfate, sodium lauryl sulfoacetate and N-acyl glutamates, e.g., N-palmitoyl glutamate, N-methylacyltaurin sodium salt, N-methylacylalanine sodium salt, sodium a-olefin sulfonate and sodium dioctylsulfosuccinate; N-alkylaminoglycerols, e.g., N-lauryldiaminoethylglycerol and N-myristyldiaminoethylglycerol, N-alkyl-N-carboxymethylammonium betaine and sodium 2-alkyl-1-hydroxyethylimidazoline betaine; polyoxyethylenealkyl ether, polyoxyethylenealkylaryl ether, polyoxyethylenelanolin alcohol, polyoxyethyleneglyceryl monoaliphatic acid ester, polyoxyethylenesorbitol aliphatic acid ester, polyoxyethylene aliphatic acid ester, higher aliphatic acid glycerol ester, sorbitan aliphatic acid ester, Pluronic type surface active agent, and polyoxyethylenesorbitan aliphatic acid esters such as polyoxyethylenesorbitan monooleate and polyoxyethylene-sorbitan monolaurate. Emulsifier-type surfactants known to those of skill in the art should be used in the compositions of this invention.

**[0027]** Examples of the binder or thickener include cellulose derivatives such as alkali metal salts of carboxymethylcellulose, methyl cellulose, hydroxyethyl cellulose and sodium carboxymethylhydroxyethyl cellulose, alkali metal al-

ginates such as sodium alginate, propylene glycol alginate, gums such as carrageenan, xanthan gum, tragacanth gum, caraya gum and gum arabic, and synthetic binders such as polyvinyl alcohol, polysodium acrylate and polyvinyl pyrrolidone.

**[0028]** Thickeners such as natural gums and synthetic polymers, as well as preservatives such as methylparaben, butyl paraben, propylparaben and phenoxyethanol, coloring agents and fragrances also are commonly included in such compositions.

**[0029]** Other active ingredients such as sunscreen materials and antimicrobial materials may be utilized in the compositions of the present invention provided that they are physically and chemically compatible with the other components of the compositions. For example, moisturizing agents such as propylene glycol, allantoin, acetamine MEA, oat protein and hyaluronic acid and other humectants may be added to the retinoid-containing formulations of this invention in order to provide moisturizing activity in conjunction with the retinoid-related activity of the products. Other proteins and amino acids may also be incorporated. Sunscreens may include organic or inorganic sunscreens, such as octylmethoxycinnamate and other cinnamate compounds, titanium dioxide and zinc oxide and the like.

**[0030]** Other ingredients may include agents which assist in protecting the skin from aging, such as sunscreens, anti-oxidant vitamins such as ascorbic acid, vitamin B, biotin, pantothenic acid, vitamin D, vitamin E and vitamin C. Yeast extract, ginkgo biloba, bisabolol, panthenol, alpha hydroxy acids and oligosaccharides such as melibiose are among other ingredients which assist in preventing aging of the skin by such means as irritation mitigation, oxidation mitigation, healing, affecting retinoid metabolism and inhibiting the production of elastase.

**[0031]** Skin color evening ingredients and depigmentation agents may also be effective in the products of this invention. Such ingredients may include hydroquinone, licorice extract, kojic acid, gatuline A (pilewort extract), micromerol (butylene glycol and apple extract), glutathione, arbutin, placenta extract, ascorbic acid, magnesium-L-ascorbyl-2-phosphate and the like.

**[0032]** Compositions which assist in the reduction of lines and wrinkles may also be added to the compositions of this invention. For example, alpha hydroxy acids, hyaluronic acid, Gatuline R (fagus silvitica extract), pigments and scattering aids such as mica, zinc oxide and titanium dioxide may be used in the compositions of this invention in this capacity. Various natural extracts such as tannins, flavenoids, saponins and the like may also be added.

**[0033]** Anti-inflammatory agents may also be used in the compositions of this invention. Not only should these agents assist in mitigating irritation, they may assist the retinoids in treating wrinkles and lines in the skin. Steroidal anti-inflammatory agents, including but not limited to, corticosteroids such as hydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethasone dipropionate, clobetasol valerate, desonide, desoxycorticosterone acetate, dexamethasone, dichlorisone, deflorasonediacetate, diflucortolone valerate, fludronolone, flucarlolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, flucionide, flucortine butylester, flucortolone, flupredidene (flupredylidene) acetate, flurandronolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenalone acetonide, medrysone, amciafel, amcinafide, betamethasone and its esters, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucoronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone and mixtures thereof may be used. Preferably, hydrocortisone may be used.

**[0034]** Nonsteroidal anti-inflammatory agents may also be employed in the compositions of this invention, such as salicylates (including alkyl and aryl esters of salicylic acid), acetic acid derivatives (including arylacetic acid and its derivatives), fenamates, propionic acid derivatives and pyrazoles or mixtures thereof. Other synthetic and natural anti-inflammatory agents may also be used.

**[0035]** Additional active ingredients having topical activity may be utilized in the compositions of this invention. Azole-type anti-fungal and anti-bacterial agents may be employed in the compositions of this invention in their base form. For example, ketoconazole, miconazole, itraconazole, metronidazole, elubiol, and like related imidazole antifungals and antibacterials are useful in the topical formulations of this invention.

**[0036]** The advantages of the invention and specific embodiments of the skin care compositions prepared in accordance with the present invention are illustrated by the following examples. It will be understood, however, that the invention is not confined to the specific limitations set forth in the individual examples, but rather to the scope of the appended claims.

#### **Example 1: An Emulsion containing A Hydrophilic Oxygen-Labile Species (Ascorbic Acid)**

**[0037]** A composition in accordance with this invention was made by combining the following ingredients in a water phase:

Ingredients	% w/w
Water	q.s. to 100%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methylparaben	0.20%
Propylparaben	0.07%
Hydroxyethyl cellulose	0.3%
Xanthan Gum	0.50%

**[0038]** A batch of 1 kilogram was made according to the following process. The weight of the beaker was recorded, and the water then added. Because this process requires boiling, an additional 50 grams of water was added to the beaker to counter the effect of evaporation. The beaker was covered with aluminum foil and beginning boiling the water. The water was permitted to boil for at least five minutes. The heat was turned off, and the water cooled to 80°C. The water phase was kept heated at least for ten minutes. The disodium EDTA was added and the water phase mixed until the EDTA was fully dissolved and clear. The xanthan gum and hydroxyethyl cellulose were slurried into the glycerin in a side container. The slurry was poured into the water phase. The preservatives were added (i.e., the phenoxyethanol, methyl paraben and propyl paraben). The water phase was held at 80°.

**[0039]** Separately, in another container, an oil phase was created using the following ingredients:

Ingredients	% w/w
Butyl hydroxytoluene	0.10%
Glyceryl monostearate & Peg-100 stearate	5.00%
Cetyl palmitate	1.00%
Cetyl alcohol	1.00%
C12-15 alkyl benzoate	4.00%
White petrolatum	1.50%
Butyl Methoxydibenzoyl methane	1.00%
Octyl methoxycinnamate	7.50%

**[0040]** All of the above named oil phase ingredients were combined in a beaker, and heated to 80°C. The oil phase was mixed homogeneously. When both phases were at 80°C, the oil was phased into the water phase. The batch was cooled to room temperature. When at 45°C, the post-additions were added to the batch.

Ingredients	%w/w
Ascorbic acid	5.00%
N-acetyl cysteine	0.10%
Ethanol	2.78%
NaOH (20%)	q.s. to desired pH.

**[0041]** The stabilizing compound, in this case the N-acetyl cysteine was added first, and allowed to mix for at least ten minutes. After the requisite mixing, the ascorbic acid was added. The sodium hydroxide was then added to neutralize the batch. The mixer speed was slowed down when the neutralization solution was added to minimize any whipping of air into the beaker. Finally, the ethanol was added, and water added to the batch q.s. The product was filled in aluminum tubes. The compositions may also be placed in any other suitable oxygen impermeable package.

#### Example 2:

**[0042]** Another composition according to this invention was made including both 2% Vitamin C and 0.1% N-acetyl cysteine. The composition included the following ingredients and was made in accordance with the method set forth in Example 1:

<u>Chemical Name</u>	<u>% wt/wt</u>
<b>Water Phase</b>	
Water	60.72%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.20%
Propyl paraben	0.07%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
<b>Oil Phase</b>	
Butylated hydroxytoluene	0.10%
Octyl methoxycinnamate	7.50%
Butyl methoxydibenzoylmethane	1.00%
Glyceryl Stearate (and) PEG-100 Stearate	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C <sub>12-15</sub> Alkyl Benzoate	4.00%
White Petrolatum	1.50%
<b>Post - additions</b>	
Ascorbic acid	5.00%
n-acetyl cysteine	0.10%
Ethanol	2.78%
NaOH (40%)	2.90%

[0043] Another formulation may also be made in accordance with this Example 2, however the 0.1% N-acetyl-cysteine may be replaced with 1% lactoferrin or iniferrin.

### Example 3:

[0044] The following is another formulation that may be made in accordance with this invention, containing ubiquinone, an anti-oxidant. The following formulation may be made in accordance with the procedure set forth in Example 1.

<u>Chemical Name</u>	<u>% wt/wt</u>
<i>Water Phase</i>	
Water	64.62%
Disodium EDTA	0.10%
Dex Panthenol	1.00%
Preservatives	0.73%
carbomer	0.35%

(continued)

Chemical Name	% wt/wt
<i>Oil Phase</i>	
Glyceryl Monostearate & PEG-100 Stearate	5.00%
Caprylic/Capric Triglycerides	3.00%
Cetyl Alcohol	2.00%
Octyl hydroxystearate	2.00%
C <sub>12-15</sub> Alkyl Benzoate	4.00%
Butyl methoxydibenzoylmethane	3.00%
Octyl methoxycinnamate	7.50%
<i>Post - Additions</i>	
Ubiquinone	0.10%
Lactoferrin (and) Thioxanthine (and) Uric Acid	0.50%
Cyclomethicone	1.50%
NaOH (10%)	4.60%
	100.00%
** adjust NaOH concentration to desired pH.	

[0045] This formulation should be stable over a period of time and under exposure to heat.

#### Example 4:

[0046] The following is another formulation that may be made in accordance with this invention, containing ascorbyl palmitate, an anti-oxidant. The following formulation may be made in accordance with the procedure set forth in Example 1.

Chemical Name	% wt/wt
<i>Water Phase</i>	
Water	64.62%
Disodium EDTA	0.10%
Glycerin	3.50%
Xanthan Gum	0.50%
Magnesium Aluminum Silicate	1.00%
Preservatives	1.00%
<i>Oil Phase</i>	
Cetearyl Glucoside	3.00%
Stearyl Alcohol	1.50%
Cetyl Alcohol	1.50%
Octyl hydroxystearate	2.00%
C <sub>12-15</sub> Alkyl Benzoate	4.00%
Dimethicone	1.00%
Ascorbyl Palmitate	0.50%
Octyl methoxycinnamate	4.00%
<i>Post - additions</i>	
N-acetyl cysteine	0.01%
Green Tea Extract	
Chamomile Extract	
NaOH (10%)	4.60%

**Example 5:**

**[0047]** The following is another formulation that may be made in accordance with this invention, containing hydroquinone, a skin-bleaching agent. The following formulation may be made in accordance with the procedure set forth in Example 1.

Chemical Name	% wt/wt
<i>Water Phase</i>	
Water	75.32%
Propylene Glycol	2.00%
Dex Panthenol	1.00%
Preservatives	0.73%
carbomer	0.35%
<i>Oil Phase</i>	
Glyceryl Monostearate & PEG-100 Stearate	5.00%
Mineral Oil	4.00%
Stearic Add	2.00%
Petrolatum	1.00%
<i>Post - Additions</i>	
Hydroquinone	2.00%
Lactoferrin (and) Thioxanthine (and) Uric Acid	2.00%
NaOH (10%)	4.60%
	100.00%
** adjust NaOH concentration to desired pH.	

**Example 6:**

**[0048]** The stability of different formulations containing retinol, ascorbic acid and/or tocopherol as set forth in Examples 7 and 8 below were monitored in terms of appearance and HPLC assay. The degraded products of retinol, ascorbic acid or tocopherol are yellow or brownish in color. The freshly prepared samples were white creams. Discoloration to yellow or brown indicates the instability.

Effect of 1% Iniferine on Retinol, Ascorbic acid and Tocopherol stability (no BHT, no EDTA)					
Example #	Active	Assay (4°C, 4 weeks)	Color (4°C, 4 weeks)	Assay (40°C, 4 weeks)	Color (40°C, 4 weeks)
Example 7	Retinol	0.168	White (no discoloration)	0.122 (72.6%)	Yellowish (discolored)
	Ascorbic acid	4.8		4.68 (97.5%)	
	Tocopherol	0.95		0.64 (67.4%)	
Example 8	Retinol	0.174	White (no discoloration)	0.165 (94.8%)	White (no discoloration)
	Ascorbic acid	4.81		4.63 (96.5%)	
	Tocopherol	1.01		0.98 (97.0%)	

**[0049]** If ascorbic acid is removed from the formulations, as set forth below, the formulations are not as stable, even with additional BHT and EDTA. However, formulations containing ascorbic acid and tocopherol were found to be stable. Thus, ascorbic acid assists in stabilizing tocopherol.

Effect of 5% Ascorbic acid on Retinol and Tocopherol stability				
Example #	active	Target value	25°C, 1 week	Color
Example 9	Retinol	0.1725	0.1695	White (no discoloration)
	Ascorbic Acid	5.00	4.96	
	Tocopherol	1.00	0.96	
Example 10	Retinol	0.1725	0.15	Bright yellow (discolored)
	Tocopherol	1.00	0.89	

[0050] Due to the immediate loss of retinol and tocopherol and significant discoloration, no further stability was conducted on Example 10. The addition of N-acetylcysteine slightly enhances the stability of retinol and tocopherol.

Effect of Ascorbic concentration on Ascorbic acid, Retinol and Tocopherol Stability (compositions referred to in Example 9)			
Initial Ascorbic concentration	active	8 weeks @ 4°C	8 weeks @ 40°C
0.1%	Retinol	0.1655 (100%)	0.1600 (96.7%)
	Ascorbic Acid	0.05 (100%)	0.04 (80%)
	Tocopherol	0.98 (100%)	1.00 (100%)
1%	Retinol	0.1582 (100%)	0.1603 (100%)
	Ascorbic Acid	0.89 (100%)	0.80 (89.9%)
	Tocopherol	0.99 (100%)	0.99 (100%)
10%	Retinol	0.1657 (100%)	0.1664 (100%)
	Ascorbic acid	9.80 (100%)	9.90 (100%)
	Tocopherol	1.10 (100%)	1.12 (100%)

[0051] If we refer to the stability of the compositions at 8 weeks at 40°C as the initial, all A (retinol), C (ascorbic acid), E (tocopherol) samples are stable. The data also suggests that it is important to control the manufacturing process for low concentration ascorbic acid to minimize any loss in stability.

#### Example 7:

[0052] A formulation according to this invention was made containing Vitamins A, C, E and iniferine. It did not include BHT, an antioxidant or disodium EDTA, a chelating agent.

Chemical Name	% wt/wt
<i>Water Phase</i>	
Water	65.15%
Disodium EDTA	0.00%
Glycerin	5.00%
Preservative	0.73%
Preservative	0.35%
Preservative	0.17%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
<i>Oil Phase</i>	
Butylhydroxytoluene	0.00%
Glyceryl Monostearate & PEG-100	5.00%

(continued)

Chemical Name	% wt/wt
<i>Oil Phase</i>	
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C <sub>12</sub> -C <sub>15</sub> Alkyl Benzoate	4.00%
White Petrolatum	1.50%
<i>Post - Additions</i>	
Ascorbic Acid	5.00%
Tocopherol	1.00%
Retinol	0.40%
Lactoferrin; thioxanthine; uric acid	0.00%
Ethanol	2.78%
NaOH (20%)	5.62%

**Example 8:**

**[0053]** A formulation according to this invention was made containing Vitamins A, C, E and iniferine. It included BHT, an antioxidant and disodium EDTA, a chelating agent.

Chemical Name	% wt/wt
<i>Water Phase</i>	
Water	64.15%
Disodium EDTA	0.00%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.35%
Propyl paraben	0.17%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
<i>Oil Phase</i>	
Butylhydroxytoluene	0.00%
Glyceryl Monostearate & PEG-100	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C <sub>12</sub> -C <sub>15</sub> Alkyl Benzoate	4.00%
White Petrolatum	1.50%
<i>Post - Additions</i>	
Ascorbic Acid	5.00%
Tocopherol	1.00%
Retinol	0.40%
Lactoferrin; thioxanthine; uric acid	1.00%
Ethanol	2.78%
NaOH (20%)	5.62%

**Example 9:**

**[0054]** Another formulation according to this invention was made containing Vitamins A, C and E but did not include sunscreens. The composition was made in accordance with the procedure set forth in Example 1.

Chemical Name	% wt/wt
<i>Water Phase</i>	
Water	63.95%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.35%
Propyl paraben	0.17%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
<i>Oil Phase</i>	
Butylhydroxytoluene	0.10%
Glyceryl Monostearate & PEG-100	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C <sub>12</sub> -C <sub>15</sub> Alkyl Benzoate	4.00%
White Petrolatum	1.50%
<i>Post-Additions</i>	
Ascorbic Acid	5.00%
Tocopherol	1.00%
Retinol	0.40%
Lactoferrin; thioxanthine; uric acid	1.00%
Ethanol	2.78%
NaOH (20%)	5.62%

**[0055]** Another 3 formulations containing 0.1%, 1% and 10% ascorbic acid respectively were made in accordance with example 9, however, 1% lactoferrin/thioxanthine/uric acid was replaced with 1% lactoferrin.

**Example 10:**

**[0056]** Yet another formulation was made in accordance with the method set forth in Example 1. This composition contained Vitamins A and E and iniferine.

Chemical Name	% wt/wt
Water	68.95%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.35%
Propyl paraben	0.17%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
Butylhydroxytoluene	0.10%

(continued)

Chemical Name	% wt/wt
Glyceryl Monostearate & PEG-100	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C <sub>12</sub> -C <sub>15</sub> Alkyl Benzoate	4.00%
White Petrolatum	1.50%
Tocopherol	1.00%
Retinol	0.40%
Lactoferrin; thioxanthine; uric acid	1.00%
Ethanol	2.78%
NaOH (20%)	5.62%

**Example 11:**

[0057] A formulation containing

Chemical Name	% wt/wt
<i>Water Phase</i>	
Water	52.85%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.35%
Propyl paraben	0.17%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
<i>Oil Phase</i>	
Butylhydroxytoluene	0.10%
Octyl methoxycinnamate Avobenzone	3.00%
Glyceryl Monostearate & PEG-100	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C <sub>12</sub> -C <sub>15</sub> Alkyl Benzoate White Petrolatum	1.50%
<i>Post - Additions</i>	
Ascorbic Acid	5.00%
Tocopherol	1.00%
Polysorbate 20	1.00%
Lactoferrin, thioxanthine, uric acid	1.00%
Ethanol	2.78%
NaOH (20%)	5.62%

**Example 12:**

[0058] A composition was made in accordance with this invention containing Vitamins A and C with Iniferine alone without N-acetyl cysteine. After 13 weeks exposure to 40°C, 95% of the Vitamin C was retained and there was no loss in A.

Chemical Name	% wt/wt
<b>Water Phase</b>	
Water	73.96%
Disodium EDTA	0.20%
Phenoxyethanol	0.73%
Methyl paraben	0.20%
Propyl paraben	0.07%
Hydroxyethylcellulose	1.00%
<b>Oil Phase</b>	
Butylhydroxytoluene	0.10%
GMS	2.00%
Cetearyl Glucoside	3.00%
C12-15 alkyl benzoate	2.00%
Avobenzone	2.00%
Octyl methoxycinnamate	4.00%
Ascorbyl Palmitate	0.50%
<b>Post - Additions</b>	
ascorbic acid	2.00%
n-acetyl cysteine	0.00%
Retinol 50c	0.27%
uric acid	1.00%
isoparaffin; laureth-7; polyacrylamide	1.50%
NaOH	5.47%

**Example 13:**

**[0059]** The following composition contained only Vitamin C with N-acetyl cysteine. It was made in accordance with the procedure set forth in Example 1 except that the composition was boiled rather than purged with inert gas to remove oxygen.

Chemical Name	% wt/wt
<b>Water Phase</b>	
Water	64.92%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.20%
Propyl paraben	0.07%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
<b>Oil Phase</b>	
Butylhydroxytoluene	0.10%
Glyceryl Monostearate & PEG-100	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%

(continued)

Chemical Name	% wt/wt
<i>Oil Phase</i>	
C12-C15 Alkyl Benzoate	4.00%
White Petrolatum	1.50%
Avobenzone	1.00%
Octyl methoxycinnamate	7.50%
<i>Post - Additions</i>	
Ascorbic Acid	2.00%
ethanol	2.78%
n-Acetyl Cysteine	0.10%
NaOH (10%)	1.70%

[0060] After exposure to 50°C for 13 weeks, 96% of the Vitamin C remained in this composition.

#### Example 14:

[0061] A composition in accordance with this invention was made using the procedure set forth in Example 1. This composition contained Vitamins A and C as well as Iniferine and N-acetyl cysteine. After 13 weeks incubation at 40°C, 90% C and 96% A remained in the composition.

Chemical Name	% wt/wt
<i>Water Phase</i>	
Water	51.27%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.35%
Propyl paraben	0.17%
Hydroxyethylcellulose	0.15%
Xanthan Gum	0.50%
<i>Oil Phase</i>	
Butylhydroxytoluene	0.10%
Octyl methoxycinnamate	7.50%
Avobenzone	3.00%
Glyceryl Monostearate & PEG-100 Stearate	5.00%
Cetyl Palmitate	1.00%
Cetyl Alcohol	1.00%
Stearyl Alcohol	0.50%
C12-C15 Alkyl Benzoates	4.00%
White Petrolatum	1.50%
<i>Post - Additions</i>	
Ascorbic Acid	5.00%
Tocopherol	0.05%
Retinol	0.25%
Lactoferrin; thioxanthine; uric acid	1.00%
n-acetyl cysteine	0.01%
Ethanol	2.78%
NaOH (20%)	9.04%

**Example 15:**

**[0062]** A composition in accordance with this invention was made using the procedure set forth in Example 1. This composition contained Vitamins A, C and E as well as Iniferine and N-acetyl cysteine. After 11.5 weeks incubation at 40°C, 92% of the Vitamin A, 99% of the Vitamin C and 97% of the Vitamin E remained in the composition.

Chemical Name	% wt/wt
<i>Water Phase</i>	
Water	53.45%
Disodium EDTA	0.10%
Glycerin	5.00%
Phenoxyethanol	0.73%
Methyl paraben	0.35%
Propyl paraben	0.17%
Hydroxyethylcellulose	0.30%
Xanthan Gum	0.50%
<i>Oil Phase</i>	
Butylhydroxytoluene	0.10%
Octyl methoxycinnamate	7.50%
Avobenzone	3.00%
Glyceryl Monostearate & PEG-100	5.00%
Octyl Hydroxystearate	2.00%
Cetyl Alcohol	2.00%
C12-C15 Alkyl Benzoate	5.00%
<i>Post - Additions</i>	
Ascorbic Acid	2.00%
Tocopherol	1.00%
Retinol	0.25%
Lactoferrin; thioxanthine; uric acid	1.00%
n-acetyl cysteine	0.01%
Cyclomethicone	1.50%
NaOH (10%)	

**[0063]** Of course, the foregoing examples are merely illustrative of the compositions and methods of this invention and do not represent its full scope.

**Claims**

- Compositions containing oil-soluble and/or water-soluble oxygen-labile species comprising oil-soluble or water-soluble oxygen-labile species and one or more stabilizer compounds selected from the group consisting of:
  - thio-containing compounds; and
  - glycoproteins.
- Compositions according to claim 1 wherein said thio-containing compounds are selected from the group consisting of sulfites, metabisulfites, glutathione and cysteine derivatives.
- Compositions according to claim 1 wherein said glycoprotein is lactoferrin.
- Compositions according to claim 3 wherein said composition further comprises thioxanthine and uric acid.
- Compositions according to claim 1 wherein said oil-soluble oxygen-labile species are selected from one or more

of the group consisting of retinoids, choleciferol, vitamin K tocotrienol, fatty acids, and tocopherol and their derivatives.

- 5 6. Compositions according to claim 1 wherein said water-soluble oxygen-labile species are selected from one or more of the group consisting of ascorbic acid and its derviatives, niacin, thiamine, riboflavin, folic acid, pyrodoxine, pantothenic acid, niacinamide, lipoic acid, dihydrolipoic acid, amino acids and their derivatives.
7. A composition according to claim 2 wherein said thio-containing compound is N-acetylcysteine.
- 10 8. Compositions according to claim 1 wherein said composition comprises one or more retinoids and one or more tocopherols and one or more ascorbic acid or its derivatives.
9. Compositions according to claim 1 wherein said composition comprises ascorbic acid and tocopherol or their derivatives.
- 15 10. A method of stabilizing compositions containing oil-soluble or water-soluble oxygen-labile species or combinations thereof comprising adding to said compositions oil-soluble or water-soluble oxygen-labile species one or more stabilizer compounds selected from the group consisting of:
  - 20 a) thio-containing compounds; and
  - b) glycoproteins.

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(11)

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(12)

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(71) Applicant: **JOHNSON & JOHNSON CONSUMER  
COMPANIES, INC.**  
**Skillman, NJ 08558 (US)**

(72) Inventors:  
• **Kung, John**  
**Somerset, New Jersey 08873 (US)**  
• **Liu, Jue-Chen**  
**Belle Mead, New Jersey 08502 (US)**

(74) Representative: **Fisher, Adrian John**  
**CARPMAELS & RANSFORD**  
**43 Bloomsbury Square**  
**London WC1A 2RA (GB)**

(54) **Compositions for stabilizing oxygen-labile species**

(57) This invention relates to compositions and methods for stabilizing oxygen-labile species. More particularly, it relates to compositions containing one or

more oil- and/or water-soluble oxygen-labile species and one or more stabilizing elements. It also relates to methods of making such compositions and methods of using such compositions.



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# EUROPEAN SEARCH REPORT

Application Number  
EP 00 30 4519

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	EP 0 280 606 A (L'OREAL) 31 August 1988 (1988-08-31) * the whole document *	1,2,5-7, 9,10	C09K15/28 C09K15/30 A61K7/48
Y	* the whole document, in particular page 2, lines 47-50 *	1,2,5-10	
Y	--- EP 0 800 825 A (BASF AG) 15 October 1997 (1997-10-15) * whole document, in particular page 3, lines 19-20 *	1,2,5-10	
Y	--- WO 97 31620 A (JOHNSON & JOHNSON CONSUMER PRODUCTS INC) 4 September 1997 (1997-09-04) * example 30 *	1,2,5,6, 8-10	
Y	--- WO 97 21423 A (THE PROCTOR & GAMBLE CO) 19 June 1997 (1997-06-19) * claims 1-4 *	1,2,5,7, 10	
X	--- WO 93 00085 A (JOHNSON AND JOHNSON CONSUMER PRODUCTS INC) 7 January 1993 (1993-01-07) * page 12, lines 1-9; examples IX, X, XIII *	1,2,5,10	TECHNICAL FIELDS SEARCHED (Int.Cl.7) C09K A61K
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 12 January 2001	Examiner Van Amsterdam, L
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			



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Application Number

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### CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

### LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:



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# EUROPEAN SEARCH REPORT

Application Number  
EP 00 30 4519

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 84:140738, XP002148542 * abstract * -& CHEMICAL ABSTRACTS, vol. 84, no. 20, 17 May 1976 (1976-05-17) Columbus, Ohio, US; abstract no. 140738, XP002148541 * abstract * & JP 49 092219 A (S.S. PHARMACEUTICAL CO LTD) ---	1,2,6,7, 10	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1990:42380, XP002148543 * abstract * & ACTA FAC. PHARM. UNIV. COMENIAE, vol. 42, 1989, pages 5-19, ---	1,2,6,7, 10	
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS 1971:440469, XP002148544 * abstract * & JP 46 009358 B (TAKEDA CHEMICAL INDUSTRIES LTD) ---	1,2,6,10	
X	DE 38 14 806 A (C. V. STEIN) 16 November 1989 (1989-11-16) * the whole document * --- -/--	1,2,6,7, 10	
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 12 January 2001	Examiner Van Amsterdam, L
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... &amp; : member of the same patent family, corresponding document</p>			



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**LACK OF UNITY OF INVENTION  
SHEET B**

Application Number  
EP 00 30 4519

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1, 5, 6, 8-10 (in part); 2, 7 (complete)

Compositions containing oxygen-labile species and one or more stabilizer compounds selected from thio-containing compounds; method of stabilizing compositions containing oxygen-labile species by adding one or more stabilizer compounds selected from thio-containing compounds

2. Claims: 1, 5, 6, 8-10 (in part); 3, 4 (complete)

Compositions containing oxygen-labile species and one or more stabilizer compounds selected from glycoproteins; method of stabilizing compositions containing oxygen-labile species by adding one or more stabilizer compounds selected from glycoproteins



European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number  
EP 00 30 4519

DOCUMENTS CONSIDERED TO BE RELEVANT				
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)	
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1990:164753, XP002148545 * abstract * & JP 01 256586 A (KOBAYASHI KOSE CO LTD) 13 October 1989 (1989-10-13) ---	1,2,5,10		
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1997:564853, XP002148546 * abstract * & JP 09 176679 A (OKAWA SHOKUHIN KOGYO KK) 8 July 1997 (1997-07-08) ---	1,2,5,10		
X	DD 150 694 A (ERNST-MORITZ-ARNDT-UNIVERSITÄT) 16 September 1981 (1981-09-16) * the whole document * ---	1,2,10		TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A,D	EP 0 349 797 A (KLINGE PHARMA GMBH) 10 January 1990 (1990-01-10) * the whole document * ---	1,2,6,7, 10		
X	FR 2 641 696 A (SEDERMA SA) 20 July 1990 (1990-07-20) * the whole document * ---	1,3-5,10		
X	FR 2 596 986 A (SEDERMA SA) 16 October 1987 (1987-10-16) * whole document, in particular page 2, lines 29-33 * Y *idem * ---	1,3,5,10		
Y		1,3,5,6, 8-10		
		-/--		
The present search report has been drawn up for all claims				
Place of search BERLIN		Date of completion of the search 12 January 2001	Examiner Van Amsterdam, L	
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document		



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# EUROPEAN SEARCH REPORT

Application Number  
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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Y	FR 2 768 623 A (T.J. NOEL) 26 March 1999 (1999-03-26) * examples 1-3 * -----	1,3,5,6, 8-10	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
The present search report has been drawn up for all claims			
Place of search <b>BERLIN</b>		Date of completion of the search <b>12 January 2001</b>	Examiner <b>Van Amsterdam, L</b>
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone  Y : particularly relevant if combined with another document of the same category  A : technological background  O : non-written disclosure  P : intermediate document</p> <p>T : theory or principle underlying the invention  E : earlier patent document, but published on, or after the filing date  D : document cited in the application  L : document cited for other reasons</p> <p>&amp; : member of the same patent family, corresponding document</p>			

**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 00 30 4519

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on  
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12-01-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 280606 A	31-08-1988	FR 2610626 A	12-08-1988
		DE 3870001 A	21-05-1992
		DE 280606 T	11-05-1989
		JP 63225689 A	20-09-1988
		US 5023235 A	11-06-1991
EP 800825 A	15-10-1997	DE 19609477 A	18-09-1997
		AU 1620497 A	18-09-1997
		CA 2199415 A	11-09-1997
		CN 1165653 A	26-11-1997
		JP 9249554 A	22-09-1997
		US 5891907 A	06-04-1999
WO 9731620 A	04-09-1997	US 5976555 A	02-11-1999
		AU 1981797 A	16-09-1997
		BR 9710405 A	17-08-1999
		CA 2247645 A	04-09-1997
		CN 1226819 A	25-08-1999
		CZ 9802715 A	14-04-1999
		EP 0885000 A	23-12-1998
		PL 328820 A	15-02-1999
WO 9721423 A	19-06-1997	AU 1128997 A	03-07-1997
WO 9300085 A	07-01-1993	AU 664973 B	14-12-1995
		AU 8299791 A	25-01-1993
		BR 9106891 A	14-06-1994
		CA 2090104 A	28-12-1992
		DE 69130020 D	24-09-1998
		DE 69130020 T	04-03-1999
		EG 19852 A	31-03-1996
		EP 0549592 A	07-07-1993
		ES 2120417 T	01-11-1998
		FI 930887 A	26-02-1993
		FI 981664 A	27-07-1998
		JP 6500079 T	06-01-1994
		MX 9100278 A	01-01-1993
		NO 304405 B	14-12-1998
		NZ 239051 A	27-02-1996
		PT 98512 A, B	30-06-1992
		SG 66224 A	20-07-1999
		US 5559149 A	24-09-1996
		US 5583136 A	10-12-1996
		US 5652263 A	29-07-1997
		ZA 9105285 A	31-03-1993

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 00 30 4519

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

12-01-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 46009358 B		NONE	
DE 3814806 A	16-11-1989	NONE	
JP 01256586 A	13-10-1989	JP 2799568 B	17-09-1998
JP 09176679 A	08-07-1997	NONE	
DD 150694 A	16-09-1981	NONE	
EP 349797 A	10-01-1990	DE 3822096 A AT 81000 T DE 58902357 D ES 2043959 T GR 3005848 T	04-01-1990 15-10-1992 05-11-1992 01-01-1994 07-06-1993
FR 2641696 A	20-07-1990	FR 2596986 A	16-10-1987
FR 2596986 A	16-10-1987	FR 2641696 A	20-07-1990
FR 2768623 A	26-03-1999	NONE	